reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The Examiner alleged that claim 11 is drawn to a pharmaceutical composition which comprises a compound which inhibits neurotoxicity in a cell by inhibiting interaction between receptor for advanced glycation end product (RAGE) and mutant presenilin-2 identified by the method of claim 1, and a pharmaceutically acceptable carrier. The Examiner alleged that the claim encompasses a genus composed of all compounds that inhibit the interaction of RAGE and mutant presenilin-2. The Examiner alleged that the specification does not disclose a single species compound that inhibits the interaction of RAGE and mutant presenilin-2. The Examiner alleged that the disclosure is not deemed sufficient to reasonably convey to one skilled in the art that applicants were in possession of a compound that inhibits the interaction of RAGE and mutant presenilin-2 at the time the applicaion was filed. The Examiner alleged that the written description requirement is not satisfied for the claimed genus. The Examiner alleged that claim 12 depends upon claim 1 and is therefore rejected for the same reason.

In response, applicants respectfully traverse the Examiner's above rejection. Nevertheless, applicants without conceding the correctness of the Examiner's position but to expedite prosecution of the subject application have hereinabove canceled claims 11-12 without prejudice or disclaimer to applicants right to pursue the subject matter of these claims in a later-filed application.

Applicants contend that canceled claims 11-12 obviate the above rejection and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Rejection under 35 U.S.C. §103(a):

The Examiner rejected claims 1, 3-5, 11-12 and 34-37 under 35 U.S.C. §103(a) as being unpatentable over Wolozin et al. taken with Yan et al. The Examiner alleged that the claimed invention is drawn to a method of evaluating the ability of a compound to inhibit neurotoxicity and pharmaceutical compositions comprising the compounds identified by the method.

The Examiner alleged that Wolozin teaches expressing presenilin-2 or mutant presenilin-2 in PC-12 cells and treating cells with amyloid-β results in increased apoptosis compared to untransfected controls. The Examiner alleged that Wolozin et al. disclose a method comprising: a) culturing the neuronally differentiated PC-12 cells in the presense or absence of a compound, i.e. pertussis toxin or amyloid-β(1-42), b) determining the level of apoptosis in the control and treated cells, and c) comparing the extent of the apoptotic activity in the cells cultured in the presence of the compound compared to cells cultured in the absence of the compound to evaluate the effect of the compound on apoptotic activity. The Examiner stated that Wolozin does not teach that PC-12 cells are transfected with a DNA sequence encoding RAGE.

The Examiner alleged that Yan teaches that enhanced expression of

RAGE in Alzheimer's disease, in affected neurons, in microglial cells and vasculature, is consistent with the concept that amyloid-β-RAGE interaction may contribute to neurotoxicity that results in dementia. The Examiner alleged that Yan indicates that RAGE can mediate amyloid-β induced oxident stress on endothelium and neuronal cells and that stress can be prevented by blocking access to RAGE using either anti-RAGE IgG or excess soluble receptor. The Examiner alleged that Yan further teach that expression of RAGE increases vulnerability to amyloid-β. The Examiner alleged that Yan teaches that RAGE, if present and/or upregulated in cells important in the pathogenesis of Alzheimer's desease, could mediate toxic effects when associated with amyloid-β. The Examiner alleged that Yan teaches transfection of RAGE into COS-1 cells and the use of these transfected cells in analyzing the effect of compounds on amyloid-β activity with respect to oxident stress.

The Examiner alleged that it would have been prima facia obvious to one of ordinary skill in the art at the time of the claimed invention was made to modify the method of Wolozin by further modifying the presenilin-2 transfected PC-12 cells of Wolozin by transfecting the cells with a vector encoding RAGE in view of the teachings of Yan et al. that cells transfected with RAGE are useful in studying the interaction of RAGE and amyloid-β on oxident stress and cytotoxicity in cells. The Examiner alleged that one of ordinary skill in the art would have been motivated to provide such a modified PC-12 cell to use in a method of identifying inhibitors of neurotoxic compounds, in view of the teachings of Yan et al.

that expression of RAGE in Alzheimer's disease, in affected neurons, in microglial, and in vasculature, is consistent with the concept that amyloid-β interaction may contribute to neurotoxicity that results in dementia. The Examiner stated that although there was no indication in either Wolozin or Yan that an interaction between amyloid-β and presenilin-2 exsisted, it would have been prima facie obvious to one of ordinary skill in the art at the time of the claimed invention was made to combine the teachings of Wolozin et al. with the teachings of Yan in order to create cells that have a greater sensitivity to amyloid-β neurotoxicity than cells expressing either mutant PS2 or RAGE, for the purpose of identifying compounds that inhibit neurotoxicity.

In response, applicants respectfully traverse the Examiner's above rejection. Applicants contend that the cited references, namely Wolozin et al. in view of Yan et al. do not render obvious the claimed invention. The prior art fails to teach or suggest any interaction between mutant PS2 and RAGE necessary for evaluating the ability of a compound to inhibit neurotoxicity. Therefore, absent the data provided in the applicants disclosure, the prior art does not provide any reasonable expectation of success that such an interaction between mutant PS2 and RAGE would be useful for identifying neuroprotective therapeutics in a cell.

Initially, applicants respectfully direct the Examiner to claim 1 which recites as follows:

A method for evaluating the ability of a compound to inhibit neurotoxicity which comprises:

(a) contacting a cell **which expresses (i) a receptor for advanced glycation end product (RAGE) protein and (ii) a mutant presenilin-2 protein** with the compound,

wherein the cell is in a cell culture and is selected from the group consisting of a neuronal cell, an endothelial cell, a glial cell, a microglial cell, an astrocyte, a neuronal tumor cell, a PC12 cell, a mononuclear cell, a mononuclear phagocyte, a smooth muscle cell, a bone cell and a myocyte, and wherein the mutant presenilin-2 protein causes increased basal apoptosis in the cell;

(b) adding amyloid-beta peptide to the cell culture to induce cell death;

(c) determining the level of cell death in the cell culture; and

(d) comparing the level of cell death determined in step (c) with the level of cell death determined in the absence of the compound so as to **evaluate the ability of the compound to inhibit n urotoxicity.**

The Examiner has conceded that there was no indication in either Wolozin et al. or Yan et al. that an interaction between RAGE and presenilin-2 (PS2) existed. See paper No. 21, page 8. Therefore, absent the data provided in the applicants disclosure, it would not have been predictable that such an interaction would be useful for identifying neuroprotective therapeutics in a cell.

Specifically, the disclosure recites that "while mutant presenilin-2 by itself has little effect on apoptosis, cells co-transfected to express mutant presenilin-2 and RAGE showed a dramatic increase in apoptosis at Aß concentrations of both 0.3 and 1µM." See page 23, lines 9-13. Further highlighting the unexpected interaction between RAGE and PS2, the specification recites "the synergistic interaction of these two factors resulted in dramatically increased apoptosis."

In contrast, while Wolozin et al. taken with Yan et al. may at most teach a role for PS2 in apoptosis and Aß-induced cellular perturbations, they neither teach nor suggests the synergistic interaction between mutant PS2 and RAGE necessary to evaluate the ability of a compound to inhibit neurotoxicity. Therefore, absent the data provided in the applicants disclosure, the prior art does not provide any reasonable expectation of success that an interaction between mutant PS2 and RAGE would be useful for identifying neuroprotective therapeutics in a cell. Accordingly, and the present invention was not obvious in view of Wolozin et al. taken with Yan et al.

Summary

For the reasons set forth hereinabove, applicants respectfully request that the Examiner reconsider and withdraw the various grounds of objection and rejection and earnestly solicit allowance of the now pending claims.